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(54) Title: METHOD FOR RAISING HDL CHOLESTEROL LEVELS

(57) Abstract

Compounds which are PPARδ agonists are described. These compounds are useful for raising high density lipoprotein (HDL) plasma levels in mammals and for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events. PPARδ agonists can be administered alone or in combination with additional active agents such as LDL-lowering agents.

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TITLE OF THE INVENTION

METHOD FOR RAISING HDL CHOLESTEROL LEVELS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in part and claims priority to of each of the following U.S provisional applications: application no. 60/011093 filed February 2, 1996 (Merck attorney docket no. 19630PV); application no. 60/------ filed December 23, 1996 (Merck attorney docket no. 19630PV2); application no. 60/011094 filed February 2, 1996 (Merck attorney docket no. 19631PV); application no. 60/------ filed December 23, 1996 (Merck attorney docket no. 19631PV2); application no. 60/011080 filed February 2, 1996 (Merck attorney docket no. 19632PV); application no. 60/------ filed December 23, 1996 (Merck attorney docket no. 19632PV2); application no. 60/011025 filed February 2, 1996 (Merck attorney docket no. 19633PV); and application no. 60/------ filed December 23, 1996 (Merck attorney docket no. 19877PV); each of which are herein incorporated by reference in their entirety.

This application is related to the following U.S. non-provisional applications: Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19630Y); Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19631Y); Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19632Y); Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19633Y); each of which are herein incorporated by reference in their entirety.

The instant invention is directed to ligands that bind to and act as agonists of the delta human peroxisome proliferator activated receptor (PPARδ). The agonists are useful for raising high density lipoprotein levels and for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events.

BACKGROUND OF THE INVENTION

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. There are five classifications of lipoproteins based on their degree of density: chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), intermediate density lipoproteins (IDL), and high density lipoproteins (HDL). These classifications are commonly known in the art and are described, for example, in the *Merck Manual*, 16th Ed. 1992 (see for example pp. 1039-1040) and "Structure and Metabolism of Plasma Lipoproteins" in *Metabolic Basis of Inherited Disease*, 6th Ed. 1989, pp. 1129-1138.

One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The initial treatment for hypercholesterolemia is often to modify the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone. LDL is commonly known as the "bad" cholesterol, while HDL is the "good" cholesterol. Although it is desirable to lower elevated levels of LDL cholesterol, it is also desirable to increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See, for example, Gordon, et al., Am. J. Med., *62*, 707-714 (1977); Stampfer, et al., N. England J. Med., *325*, 373-381 (1991); and Kannel, et al., Ann. Internal Med., *90*, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL raising are associated with undesirable effects, such as flushing.

Peroxisome proliferators are a structurally diverse group of compounds that when administered to rodents elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes of the

beta-oxidation cycle. Compounds of this group include but are not limited to the fibrate class of hyperlipidemic drugs, herbicides and phthalate plasticizers. Peroxisome proliferation is also triggered by dietary or physiological factors such as a high-fat diet and cold acclimatization.

Three sub-types of peroxisome proliferator activated receptor (PPAR) have been discovered and described; they are peroxisome proliferator activated receptor alpha (PPARα), peroxisome proliferator activated receptor gamma (PPARγ) and peroxisome proliferator activated receptor delta (PPARδ). Identification of PPARα, a member of the nuclear hormone receptor superfamily activated by peroxisome proliferators, has facilitated analysis of the mechanism by which peroxisome proliferators exert their pleiotropic effects. PPARα is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β–oxidation of fatty acids. PPARα is also involved with the activity of fibrates and fatty acids in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

The PPARγ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. There are two isoforms of PPARγ: PPARγ1 and PPARγ2, which differ only in that PPARγ2 contains an additional 28 amino acids present at the amino terminus. The DNA sequences for the isotypes are described in Elbrecht, et al., BBRC *224*;431-437 (1996). In mice, PPARγ2 is expressed specifically in fat cells. Tontonoz *et al.*, *Cell 79*: 1147-1156 (1994) provide evidence to show that one physiological role of PPARγ2 is to induce adipocyte differentiation. As with other members of the nuclear hormone receptor superfamily, PPARγ 2 regulates the expression of genes through interaction with other proteins and binding to hormone response elements for example in the 5' flanking regions of responsive

genes. An example of a PPARγ2 responsive gene is the tissue-specific adipocyte P2 gene. Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J2 derivatives have been identified as natural ligands of the PPARγ subtype, which also binds thiazolidinedione antidiabetic agents with high affinity.

The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, *6* :1634-1641 (1992), herein incorporated by reference. It should be noted that PPARδ is also referred to in the literature as PPARβ and as NUC1, and each of these names refers to the same receptor; in Schmidt et al, the receptor is referred to as NUC1.

In WO96/01430, a human PPAR subtype, hNUC1B, is disclosed. The amino acid sequence of hNUC1B differs from human PPARδ (referred to therein as hNUC1) by one amino acid, i.e., alanine at position 292. Based on in vivo experiments described therein, the authors suggest that hNUC1B protein represses hPPARα and thyroid hormone receptor protein activity.

However, prior to the instant invention, no function had been identified for the PPARδ subtype. Applicants have now discovered that ligands which are agonists of PPARδ are useful for raising HDL levels. Since there is a continued need for methods to increase HDL levels in mammals, particularly humans, the present invention addresses this need by providing novel methods and compounds useful for raising HDL.

SUMMARY OF THE INVENTION

One object of this invention is to provide a method for raising high density lipoprotein (HDL) plasma levels in a mammal in need of such treatment comprising administering an HDL-raising amount of a PPARδ agonist.

A second object is to provide methods for preventing, halting or slowing the progression of atherosclerotic cardiovascular

diseases and related conditions and disease events in a mammal in need of such treatment comprising administering an HDL-raising amount of a PPARδ agonist.

A third object is to provide methods for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events in a mammal in need of such treatment comprising administering an HDL-raising amount of a PPARδ agonist in combination with one or more additional active agents, for example an hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.

A fourth object is to describe and provide compounds which are PPARδ agonists and which are useful for the above-described methods. Additional objects will be evident from the following description.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the instant invention are those which activate and therefore are agonists of PPARδ. All compounds which can be determined to be agonists of PPARδ using scientifically sound in vitro or in vivo assay procedures are intended to be within the scope of this invention. More particularly, PPARδ agonists which are intended to be within the scope of this invention are those which have (1) an IC_{50} equal to or less than 10 μM in the hPPARδ binding assay, and (2) an EC_{50} equal to or less than 10 μM in the hPPARδ transactivation assay. Preferably, the PPARδ agonists have an IC_{50} equal to or less than 100 nM in the hPPARδ binding assay, and an EC_{50} equal to or less than 100 nM in the hPPARδ transactivation assay. More preferably, the PPARδ agonists have an IC_{50} equal to or less than 50 nM in the hPPARδ binding assay, and an EC_{50} equal to or less than 50 nM in the hPPARδ transactivation assay. Most preferably, the PPARδ agonists have an IC_{50} equal to or less than 10 nM in the hPPARδ binding assay, and an EC_{50} equal to or less than 10 nM in the hPPARδ transactivation assay. Compounds which are PPARδ agonists as defined above may also have activity at the PPARγ or PPARα receptors.

The hPPARδ binding assay comprises the steps of:

(a) preparing multiple test samples by incubating separate aliquots of the receptor hPPARδ with a test compound in TEGM containing 5-10% COS-1 cell cytoplasmic lysate and 2.5 nM labeled ([$^3H_2$]Compound D, 17 Ci/mmole) for a minimum of 12 hours, and preferably for about 16 hours, at 4 °C, wherein the concentration of the test compound in each test sample is different, and preparing a control sample by incubating a further separate aliquot of the receptor hPPARδ under the same conditions but without the test compound; then

(b) removing unbound ligand by adding dextran/gelatin-coated charcoal to each sample while maintaining the samples at 4 °C and allowing at least 10 minutes to pass, then

(c) subjecting each of the test samples and the control sample from step (b) to centrifugation at 4 °C until the charcoal is pelleted; then

(d) counting a portion of the supernatant fraction of each of the test samples and the control sample from step (c) in a liquid scintillation counter and analyzing the results to determine the IC_{50} of the test compound.

In the hPPARδ binding assay, preferably at least four test samples of varying concentrations of a single test compound are prepared in order to determine the IC_{50}.

The hPPARδ transactivation assay comprises the steps of:

(a) seeding an hPPARδ/GR stable CHO-K1 cell line into alpha MEM containing 10% FCS, 10 mM HEPES, and 500 mg/ml G418 at 37°C in an atmosphere of 10% CO_2 in air,

(b) incubating the cells from step (a) for 16 to 48 hours, preferably about 20 hours, at 37°C in an atmosphere of 10% CO_2 in air;

(c) washing the cells from step (b) with alpha MEM;

(d) preparing multiple test cell groups by incubating separate groups of the cells from step (c) with the test compound in alpha MEM containing 5% charcoal stripped FCS, 10 mM HEPES, and 500 mg/ml G418, for 24 to 48 hours, preferably about 24 hours, at 37°C in an atmosphere of 10% CO_2 in air, wherein the concentration of

the test compound in each test cell group is different, and preparing a control cell group by incubating a further separate group of the cells from step (c) under the same conditions but without the test compound; then

(e) preparing cell lysates from each of the test cell groups and the control cell group of step (d) using an aqueous detergent lysis buffer, and

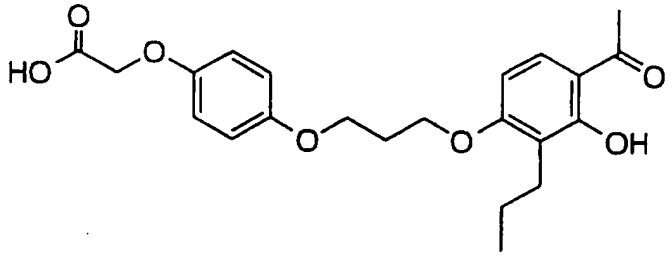
(f) measuring the luciferase activity of the test cell groups and the control cell group of step (e) and analyzing the results to determine the EC_{50} of the test compound.

In the hPPARδ transactivation assay, preferably at least four test cell groups of varying concentrations of a single test compound are prepared in order to determine the EC_{50}.

Specific examples of the hPPARδ binding assay and the hPPARδ transactivation assay are described below in Examples 1B and 3B, respectively.

Examples of compounds which are PPARδ agonists include, but are not limited to, the following compounds A through F and the pharmaceutically acceptable salts and esters thereof:

A)



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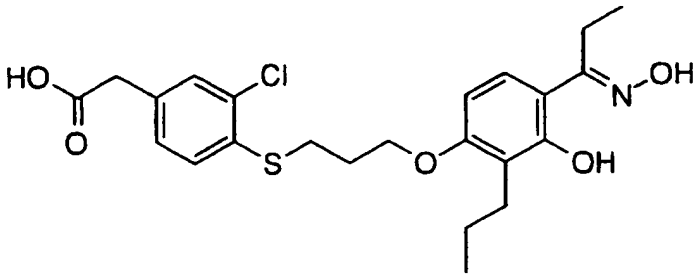
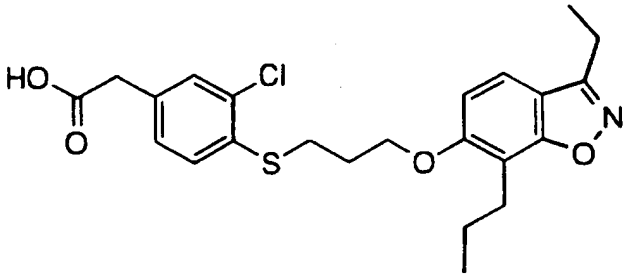
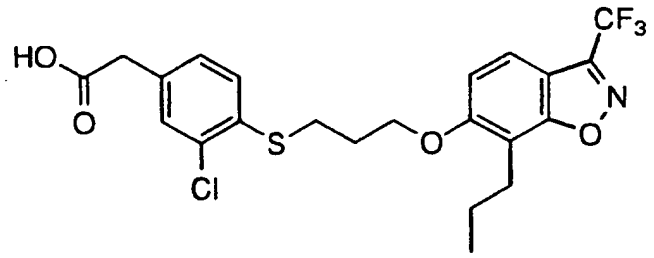


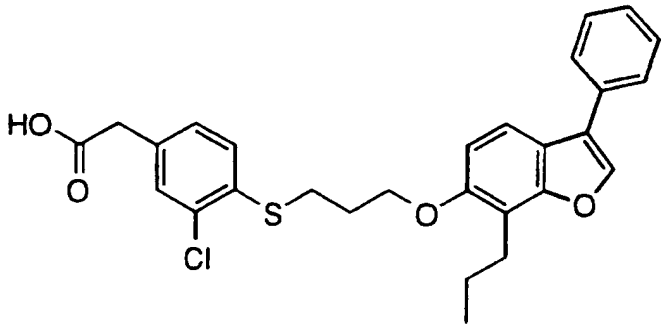
C)



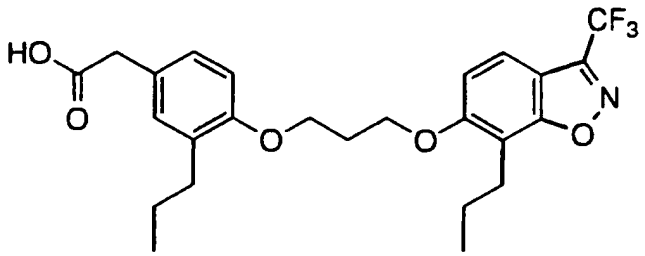
D)



E)



and F)



Additional compounds which are PPARδ agonists and are included within the scope of this invention include but are not limited to those found in the following U.S provisional applications: application no. 60/011093 filed February 2, 1996 (Merck attorney docket no. 19630PV); application no. 60/------ filed December 23, 1996 (Merck attorney docket no. 19630PV2); application no. 60/011094 filed February 2, 1996 (Merck attorney docket no. 19631PV); application no. 60/------ filed December 23, 1996 (Merck attorney docket no. 19631PV2); application no. 60/011080 filed February 2, 1996 (Merck attorney docket no. 19632PV); application no. 60/------ filed December 23, 1996 (Merck attorney docket no. 19632PV2); application no. 60/011025 filed February 2, 1996 (Merck attorney docket no. 19633PV); and application no. 60/------ filed December 23, 1996

(Merck attorney docket no. 19877PV); each of which are herein incorporated by reference in their entirety.

Additional compounds which are PPARδ agonists and are included within the scope of this invention include but are not limited to those found in the following U.S non-provisional applications: Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19630Y); Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19631Y); Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19632Y); and Serial No. --/------ filed January 31, 1997 (Merck attorney docket no. 19633Y); each of which are herein incorporated by reference in their entirety.

The instant invention provides methods for preventing or reducing the risk of developing atherosclerosis, comprising the administration of a prophylactically effective amount, or more particularly an HDL-raising amount, of a PPARδ agonist, alone or in combination with one or more additional pharmaceutically active agents, to a mammal, particularly human, who is at risk of developing atherosclerosis.

PPARδ agonists can also be used in methods for treating, halting or slowing the progression of atherosclerotic disease once it has become clinically evident, comprising the administration of a therapeutically effective amount, or more particularly an HDL-raising amount, of a PPARδ agonist, alone or in combination with one or more additional pharmaceutically active agents, to a mammal, particularly human, who already has atherosclerotic disease.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

The instant invention further provides methods for preventing or reducing the risk of a first or subsequent (where the potential exists for recurrence) atherosclerotic disease event, comprising the administration of a prophylactically effective amount, or more particularly an HDL-raising amount, of a PPARδ agonist, alone or in combination with one or more additional pharmaceutically active agents, to a mammal, particularly human, who is at risk for having an atherosclerotic disease event. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease event are those for whom the potential for recurrence of such an event exists.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited to hypertension, smoking, diabetes, low levels of high density lipoprotein cholesterol, high levels of low density lipoprotein cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on *Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)*, National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; *abbreviated version:* Expert Panel on Detection, Evaluation, and

Treatment of High Blood Cholesterol in Adults, *Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II), JAMA*, 1993, *269*, pp. 3015-23. People who are identified as having one or more of the above-noted risk factors are intended to be included in the group of people considered at risk for developing atherosclerotic disease. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease event.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, in specified amounts where amounts are specified, as well as any product which results directly or indirectly from combination of the specified ingredients, in the specified amounts where amounts are specified.

The active PPARδ agonist compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. The active compounds can also be administered intranasally as, for example, liquid drops or spray. Oral administration is preferred. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit.

Therapeutically effective amounts, prophylactically effective amounts and/or high density lipoprotein-raising amounts of the PPARδ agonist are suitable for use in the compositions and methods of

the present invention. The term "therapeutically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a clinician, such as a researcher, veterinarian, medical doctor or osteopathic doctor.

The term "prophylactically effective amount" is intended to mean that amount of a drug or pharmaceutical agent that will prevent or reduce the risk of occurrence of a medical condition, such as atherosclerosis or an atherosclerotic disease event.

The term "high density lipoprotein-raising amount" is intended to mean an amount of a drug or pharmaceutical agent that will elevate a subject's plasma HDL level above the level it was at prior to administration of the drug or pharmaceutical agent. Measurement of plasma HDL levels can be performed using any medically acceptable procedures known to those skilled in the medical arts, including assay kits designed for use directly by consumers.

The dosage regimen utilizing a PPARδ agonist is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or derivative thereof employed. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining an appropriate HDL-raising amount of the PPARδ agonist, as well as the therapeutically effective amounts of the PPARδ agonist needed to prevent, counter, or arrest the progress of the condition.

For example, the compounds of the present invention can be administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, once a day or given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligram to about 1000 milligrams, preferably from about 1 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350

milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

In the above-described methods, the PPARδ agonist may be administered alone or in combination with one or more additional active agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a PPARδ agonist and one or more additional active agents, as well as administration of the PPARδ agonist and each active agent in its own separate pharmaceutical dosage formulation. For example, a PPARδ agonist and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the PPARδ agonist and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e, sequentially; combination therapy is understood to include all these regimens.

For example, the PPARδ agonist may be administered in combination with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent such as a cholesterol biosynthesis inhibitor, for example an HMG-CoA reductase inhibitor, an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitor such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor such as beta-sitosterol; a bile acid sequestrant anion exchange resin such as cholestyramine, colestipol or a dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates such as clofibrate, fenofibrate, and gemfibrizol; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); anti-oxidant vitamins such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation

inhibitor such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin. As noted above, the PPARδ agonist can be administered in combination with more than one additional active agent, for example, a combination of PPARδ agonist with an HMG-CoA reductase inhibitor and aspirin, or PPARδ agonist with an HMG-CoA reductase inhibitor and a beta blocker.

The PPARδ agonist is preferably administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt, ester, free acid and lactone forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, free acids and lactone forms is included within the scope of this invention. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see US Patent No. 4,231,938), simvastatin (ZOCOR®; see US Patent No. 4,444,784), pravastatin sodium (PRAVACHOL®; see US Patent No. 4,346,227), fluvastatin sodium (LESCOL®; see US Patent No. 5,354,772), atorvastatin calcium (LIPITOR®; see US Patent No. 5,273,995) and rivastatin (also known as cerivastatin; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996). Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or

similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the *Physicians' Desk Reference* (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA reductase inhibitor is from about 1 to 200 mg/day, and more preferably from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA RI which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg; for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of from 1 mg to 160 mg, and more particularly from 5 mg to 80 mg. Oral administration may be in single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

In accordance with this invention, an HDL-raising amount of a PPARδ agonist can be used for the preparation of a medicament useful for raising the plasma level of high density lipoprotein in mammals, particularly in humans. Furthermore, a prophylactically effective amount of a PPARδ agonist can be used for the preparation of a medicament useful for preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. Also, a therapeutically effective amount of a PPARδ agonist can be used for the preparation of a medicament useful for treating atherosclerosis in mammals, particularly in humans.

Additionally, in the preparation of the above-described medicaments, the PPARδ agonist can be admixed together with a therapeutically effective amount of one or more additional active agents selected from the group consisting of: an LDL-lowering agent; an antihyperlipidemic agent; an HDL-raising agent; an HMG-CoA synthase inhibitor; a squalene epoxidase inhibitor; a squalene synthetase inhibitor ; an acyl-coenzyme A: cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; and aspirin.

In particular, the PPARδ agonist and a therapeutically effective amount of an HMG-CoA reductase inhibitor can be admixed together for the preparation of a medicament useful for the above-described treatments. More particularly, the PPARδ agonist and a therapeutically effective amount of an HMG-CoA reductase inhibitor selected from the pharmaceutically acceptable lactone, free acid, ester and salt forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin can be admixed together for the preparation of a medicament suitable for oral administration which is useful for the above-described treatments. Most particularly, the HMG-CoA reductase inhibitor used for the medicament preparation is lovastatin or simvastatin.

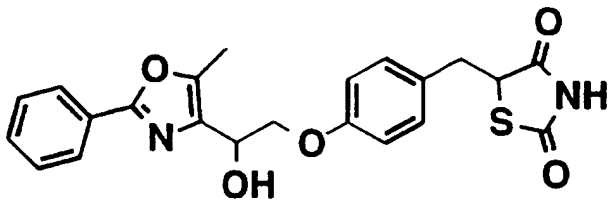
Compounds which are PPARδ agonists within the scope of this invention can be identified by the following procedures. To evaluate IC_{50} or EC_{50} values the compounds were titrated in the appropriate assay using different concentrations of the compound to be tested. To obtain the appropriate values (%Inhibition-IC_{50}, or %Activation-EC_{50}), the data resulting from the assays were then analyzed by determining the best fit of a 4 parameter function to the

data using the Levenberg-Marquardt non-linear fitting algorithm in Kaleidagraph (Synergy Software, Reading, PA).

The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., Molecular Endocrinology, *6* :1634-1641 (1992), herein incorporated by reference in its entirety.

Particular terms and abbreviations used herein are defined as follows: gst is glutathione-S-transferase; EDTA is ethylenediaminetetraacetic acid; HEPES is N-[2-hydroxyethyl]-piperazine-N'-[2-ethanesulfonic acid]; FCS is fetal calf serum; Lipofectamine is a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(spermine-carboxamido)ethyl]-N,N-dimethyl-1-propanaminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in water; G418 is geneticin; MEM is Minimum Essential Medium; Opti MEM 1 Reduced-Serum Medium is an aqueous composition containing HEPES buffer, 2400 mg/L sodium bicarbonate, hypoxanthine, thymidine, sodium pyruvate, L-glutamine, trace elements, growth factors, and phenol red reduced to 1.1 mg/L; Luciferase Assay Reagent (in re-constituted form) is an aqueous composition containing 20 mM tricine, 1.07 mM $(MgCO_3)_4Mg(OH)_2 \cdot 5H_2O$, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 33.3 mM DTT, 270 μM coenzyme A, 470 μM luciferin, 530 μM ATP, having a final pH of 7.8.

AD-5075 has the following structure:



AD-5075 (Takeda)

Compound D can also be used in place of AD-5075 in the hPPARγ2 binding assay.

Opti MEM 1 Reduced-Serum Medium, alpha MEM, G418, and Lipofectamine are commercially available from GibcoBRL Life

Technologies, Gaithersburg, Maryland. Alpha MEM is an aqueous composition having the following components:

Component: Inorganic Salts	**mg/L**
$CaCl_2$ (anhyd.)	200.00
$CaCl_2 \cdot 2H_2O$	--
KCl	400.00
$MgSO_4$ (anhyd.)	97.67
$MgSO_4 \cdot 7H_2O$	--
NaCl	6800.00
$NaHCO_3$	2200.00
$NaH_2PO_4 \cdot H_2O$	140.00
$NaH_2PO_4 \cdot 2H_2O$	--
Other Components:	**mg/L**
D-Glucose	1000.00
Lipoic Acid	0.20
Phenol Red	10.00
Sodium Pyruvate	110.00
Amino Acids:	**mg/L**
L-Alanine	25.00
L-Arginine•HCl	126.00
L-Asparagine•H_2O	50.00
L-Aspartic Acid	30.00
L-Cystine	--
L-Cystine•2HCl	31.00
L-Cysteine HCl	--
L-Cysteine HCl•H_2O	100.00

L-Glutamic Acid	75.00
L-Glutamine	292.00
L-Alanyl-L-Glutamine	--
Glycine	50.00
L-Histidine HCl•H_2O	42.00
L-Isoleucine	52.00
L-Leucine	52.00
L-Lysine•HCl	73.00
L-Methionine	15.00
L-Phenylalanine	32.00
L-Proline	40.00
L-Serine	25.00
L-Threonine	48.00
L-Tryptophan	10.00
L-Tyrosine	--
L-Tyrosine (disodium salt)	52.00
L-Valine	46.00
Vitamins:	**mg/L**
L-Ascorbic acid	50.00
Biotin	0.10
D-Ca Pantothenate	1.00
Choline Chloride	1.00
Folic acid	1.00
i-Inositol	2.00
Niacinamide	1.00
Pyridoxal HCl	1.00
Riboflavin	0.10

Thiamine HCl	1.00
Vitamin B_{12}	1.40
Ribonucleosides	**mg/L**
Adenosine	10.00
Cytidine	10.00
Guanosine	10.00
Uridine	10.00
Deoxyribonucleosides	**mg/L**
2' Deoxyadenosine	10.00
2' Deoxycytidine HCl	11.00
2' Deoxyguanosine	10.00
Thymidine	10.00

EXAMPLE 1A

Preparation of Human PPARδ

Human PPARδ was prepared as a gst-fusion protein in *E. coli*. The full length human cDNA for PPARδ was subcloned into the PGEX-KT expression vector (Pharmacia). *E. coli* containing the plasmid were grown, induced, and then harvested by centrifugation. The resuspended pellet was broken in a French press and debris was removed by centrifugation at 12,000Xg. Receptor was purified from the supernatant by affinity chromatography on glutathione sepharose. After application to the column, and 1 wash the receptor was eluted with glutathione. Glycerol was added to stabilize the receptor and aliquots were frozen at -80 °C for later use.

EXAMPLE 1B
hPPARδ BINDING ASSAY

[^{3}H]Compound D Displacement Assay (PPARδ)

For each assay, an aliquot of receptor from Example 1A (1:1000-1:3000 dilution) was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 µl/100 ml ß-mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreotol, 5 µg/ml aprotinin, 2 µg/ml leupeptin, 2 µg/ml benzamide and 0.5 mM phenylmethylsulfonylfluoride) containing 5-10% COS-1 cell cytoplasmic lysate and 2.5 nM labeled ([$^3H_2$]Compound D, 17 Ci/mmole), with or without test compound (incubation without test compound serves as the control for comparison purposes). Assays were incubated for about 16 hours at 4 °C in a final volume of 300 µl. Unbound ligand was removed by addition of 200 µl dextran/gelatin-coated charcoal, on ice, for about 10 minutes. After centrifugation at 3000 rpm for 10 min at 4 °C, 200 µl of the supernatant fraction was counted in a liquid scintillation counter. In this assay the K_D for Compound D is about 1 nM.

EXAMPLE 2A

Preparation of Human PPARγ2

Human PPARγ2 was prepared as a gst-fusion protein in *E. coli*. The full length human cDNA for PPARγ2 was subcloned into the PGEX-2T expression vector (Pharmacia). *E. coli* containing the plasmid were propagated, induced, and then harvested by centrifugation. The resuspended pellet was broken in a French press and debris was removed by centrifugation at 12,000Xg. Recombinant human PPARγ2 receptor was purified from the supernatant by affinity chromatography on glutathione sepharose. After application to the column, and 1 wash, receptor was eluted with glutathione. Glycerol was added to stabilize the receptor and aliquots were frozen at -80 °C for later use.

EXAMPLE 2B
hPPARγ2 BINDING ASSAY

[^{3}H]AD-5075 Displacement Assay (PPARγ2)

For each assay, an aliquot of receptor from Example 2A (1:1000-1:3000 dilution) was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 µl/100 ml ß-mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 µg/ml aprotinin, 2 µg/ml leupeptin, 2 µg/ml benzamide and 0.5 mM phenylmethylsulfonylfluoride) containing 5-10% COS-1 cell cytoplasmic lysate and 10 nM labeled thiazolidinedione ([$^3H_2$]AD-5075, 21 Ci/mmole), with or without test compound (incubation without test compound serves as the control for comparison purposes). Assays were incubated for about 16 hours at 4 °C in a final volume of 300 µl. Unbound ligand was removed by addition of 200 µl dextran/gelatin-coated charcoal, on ice, for about 10 minutes. After centrifugation at 3000 rpm for 10 min at 4 °C, 200 µl of the supernatant fraction was counted in a liquid scintillation counter. In this assay the K_D for AD-5075 is about 1 nM.

EXAMPLE 3A

A. Plasmids

The chimeric receptor expression construct, pSG5-hPPARδ/GR, was prepared by inserting the DNA binding domain of the murine glucocorticoid receptor adjacent to the ligand binding domain of hPPARδ. The glucocorticoid receptor-responsive reporter vector, pMMTV/luc/neo, contains the murine mammary tumour virus (MMTV) promoter adjacent to the luciferase gene (luc) and the neomycin resistance gene (neo). It was constructed from pMMTV/luc. Prior to transfection into CHO-K1 cells, pSG5-hPPARδ/GR was linearized with Xba I. pMMTV/luc/neo DNA was cut with Pvu I. The PPAR-responsive reporter construct, pPPRE-luc, contained 3 copies of a generic PPRE placed adjacent to the thymidine kinase minimal promoter and the luciferase reporter gene. The transfection control vector, pCMV-lacZ, contains the galactosidase Z gene under the regulation of the cytomegalovirus promoter.

B. Production of stable cell lines

CHO-K1 cells were seeded overnight at $6x10^5$ cells /60 mm dish in alpha MEM additionally containing 10% FCS, 10 mM HEPES, 100 units/ml PenicillinG and 100 µg/ml Streptomycin sulfate, at 37°C in an atmosphere of 10% CO_2 in air. The cells were washed once with Opti MEM 1 Reduced-Serum Medium and then cotransfected with 4.5 µg of pSG5-hPPARδ/GR expression vector and 0.5 µg of pMMTV/luc/neo in the presence of 100 µg Lipofectamine (Gibco-BRL, Gaithersburg, MD) according to the instructions of the manufacturer. Transfection medium was removed 2 hours later and replaced with growth medium. After being incubated for 3 days, cells were subcultured by diluting the cell suspension 1/1250 and 1/6250 and placing the cells in a 100 mm culture dish. Selection of the stable cell lines was initiated the next day by adding 500 µg/ml G418 to the medium. Cells were routinely fed with the selection media for 1 month at which time 120 colonies were picked and transferred to 24 well culture plates. Ten days later, confluent colonies were transferred to a 6 well plate to maintain stocks and to 96 well plates to assay for luciferase activity. Positive clones were characterized and validated by titrating 4 known agonists on each clone. Two clones, g2B2P2D9 and d2A5P2G3, were selected for screening purposes.

EXAMPLE 3B
hPPARδ TRANSACTIVATION ASSAY

hPPARδ/GR transactivation screens in stably transfected CHO-K1 cells

The hPPARδ/GR stable CHO-K1 cell lines from Example 3A were seeded at $1x10^4$ cells/well into 96 well cell culture plates in alpha MEM containing 10% FCS, 10 mM HEPES, and 500 mg/ml G418 at 37°C in an atmosphere of 10% CO_2 in air. After a 20 hour incubation, cells were washed once with alpha MEM and then incubated at 37°C in an atmosphere of 10% CO_2 in air in alpha MEM containing 5% charcoal stripped FCS, 10 mM HEPES, and 500 mg/ml G418. The cells were incubated for 24 hours in the absence of test compound or in

the presence of a range of concentrations of test compound. Cell lysates were prepared from washed cells using Reporter Lysis Buffer (Promega) according to the manufacturer's directions. Luciferase activity in cell extracts was determined using Luciferase Assay Reagent buffer (Promega) in a ML3000 luminometer (Dynatech Laboratories).

EXAMPLE 4A

A. Plasmids

The chimeric receptor expression construct, pSG5-hPPARγ2/GR was prepared, and the production of stable cell lines was performed, according to the procedures described in Example 3A, except that hPPARγ2 was substituted for the hPPARδ used therein.

EXAMPLE 4B
hPPARγ2 TRANSACTIVATION ASSAY

hPPARγ2/GR transactivation screens in stably transfected CHO-K1 cells

The assay is performed as described in Example 3B, except that hPPARγ2/GR stable CHO-K1 cell lines are employed in place of the hPPARδ/GR stable CHO-K1 cell lines.

Table 1, below, shows the results of the hPPARδ and hPPARγ2 binding assay and transactivation assay for the listed compounds.

TABLE 1

Compound	Binding (IC_{50}, nM)		Transactivation (EC_{50}, nM)	
	gst-hPPARδ	gst-hPPARγ2	hPPARδ/GR	hPPARγ2/GR
Compound A	40	8,000	90	10,000
Compound B	7	51	5	400
Compound C	8	171	22	650
Compound F	2	724	2	2,300
Compound E	7	23	4	500
Compound D	3	2	5	800

EXAMPLE 5

A. Plasmids

The wild type receptor construct, pSG5-hPPARγ2 was prepared by inserting the full-length hPPARγ2 cDNA adjacent to the SV40 promoter in pSG5. The wild type receptor construct, pJ3-hPPARδ, was prepared by placing the hPPARδ cDNA adjacent to the SV40 promoter in pJ3 omega.

B. Characterization of ligand activity on wild-type hPPARγ2 and hPPARδ

COS-1 cells were seeded at 0.5 X 10^5 cells/dish into 24 well plates in Dulbecco's modified Eagle medium (high glucose) containing 10% charcoal stripped fetal calf serum, nonessential amino acids, 100 units/ml Penicillin G and 100 µg/ml Streptomycin sulfate at 37°C in a humidified atmosphere of 10% CO_2. After 24 hours, transfections were performed with Lipofectamine (Gibco-BRL,

Gaithersburg, MD) according to the instructions of the manufacturer. In general, for transactivation experiments, transfection mixes contained 0.15 mg of hPPARγ2 or hPPARδ expression vector, 0.15 mg of reporter vector pPPRE-luc and 0.001 mg of pCMV-lacZ as an internal control of transfection efficiency. Compounds demonstrating significant agonist activity in the above primary screen were further characterized by incubation with transfected cells for 48 hours across a range of concentrations. Luciferase activity was determined as described above.

In a similar manner, hPPARγ1 cDNA can be used in place of hPPARγ2 cDNA in the methods described in Example 5 to make the wild type receptor construct, pSG5-hPPARγ1.

EXAMPLE 6
IN VIVO STUDIES

Methods:

db/db Mice are obese, highly insulin resistant animals. The db locus has been shown to code for the leptin receptor. These animals are substantially hypertriglyceridemic and hyperglycemic.

Male db/db mice (10-11 week old C57Bl/KFJ, Jackson Labs, Bar Harbor, ME) were housed 5/cage and allowed *ad lib.* access to ground Purina rodent chow and water. The animals, and their food, were weighed every 2 days and were dosed daily by gavage with vehicle (0.5% carboxymethylcellulose) alone or with vehicle containing test compound at the indicated dose. Drug suspensions were prepared daily. Plasma glucose, triglyceride, and cholesterol concentrations were determined from blood obtained by tail bleeds at 3-5 day intervals during the study period. Glucose, triglyceride, and cholesterol determinations were performed on a Boehringer Mannheim Hitachi 911 automatic analyzer (Boehringer Mannheim, Indianapolis, IN) using heparinized plasma diluted 1:5, or 1:6 (v/v) with normal saline. Lean

animals were age-matched heterozygous mice maintained in the same manner.

Lipoprotein analysis was performed on either serum, or EDTA treated plasma obtained by heart puncture from anesthetized animals at the end of the study. Apolipoprotein concentrations were determined by ELISA, and cholesterol particles were analyzed by FPLC, precipitation, or ultracentrifugation. Total liver RNA was prepared from tissue that had been frozen on liquid nitrogen at the time of euthanasia. Apolipoprotein mRNA was analyzed on Northern Blots using specific probes for rat proteins.

Cholesterol measurements:

A. Precipitation

HDL was separated from apo B-containing lipoproteins by dextran sulfate precipitation. Cholesterol was measured enzymatically using a commercially available cholesterol kit (Boehringer Mannheim Biochemicals, Indianapolis, IN) and spectrophotometrically quantitated on a microplate reader (EL 311; Bio-Teck Instruments, Winooski, VT).

B. Ultracentrifugation

Lipoproteins were separated according to the method of Havel (RJ Havel, HA Eder, and JH Bragdon, "The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum.," J. Clin. Invest. 1955, 34:1345-1353). Briefly, samples are fractionated on potassium bromide density gradients spun at 40,000 rpm, 4 °C, for 24 hours. Densities are adjusted according to the formula:

$g(KBr) = (\text{Initial Volume}(d_{final} - d_{initial}))/1-(d_{final} \times 0.312)$.

Lipoprotein fractions are defined as follows:

VLDL: $d<1.006$ kg/L

LDL: $1.006 < d < 1.063$ kg/L

HDL: $1.063 < d < 1.210$ kg/L

Table 2, below, shows the ratio of HDL cholesterol to the sum of VLDL + LDL cholesterol for db/db mice treated for 12 days (once daily dosing by oral gavage) with the indicated compound. Values shown represent the mean of 2 pools of serum each made from 4-5 individual animals. Determinations performed both on lipoprotein particles separated by ultracentrifugation and by precipitation of non-HDL cholesterol from whole serum. BRL 49653 is a known PPARγ selective agent (see J. Med. Chem. 1994, *37*:3977-3985).

TABLE 2

Ratio of (HDL Cholesterol) / (VLDL+LDL Cholesterol).

	db/db control	BRL 49653	Compound A		Compound F	
		30 mpk	10 mpk	30 mpk	10 mpk	30 mpk
Ultracentrifu-gation	2.89	1.83	3.59	4.18	3.11	3.18
Precipitation	2.06	1.29	2.95	3.1	2.16	2

Table 3, below, shows the serum values following 14 days of dosing in the same experiment as described above for table 2.

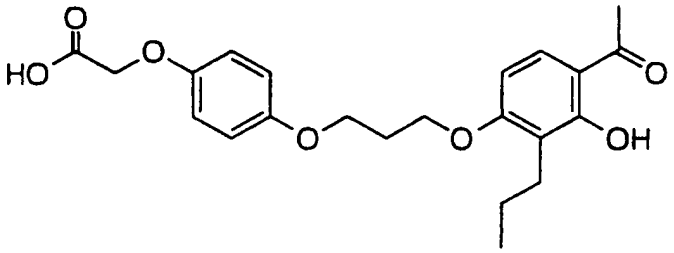
TABLE 3

Serum Concentrations of Cholesterol, HDL Cholesterol

	Treatment	
	db/db control	Compound A
Cholesterol	1.56 ± 0.18	1.72 ± 0.10*
HDL-cholesterol	1.05 ± 0,20	1.3 ± 0.09**

EXAMPLE 7

Preparation of 4-(3-(2-propyl-3-hydroxy-4-acetyl-phenoxy)propyloxy)-phenoxy acetic acid



Step 1: Preparation of methyl 4-hydroxyphenoxyacetate

Commercially available 4-hydroxyphenoxyacetic acid (2 g) was dissolved in methanol (10 ml) with approximately 0.04 ml H_2SO_4 conc. The mixture was heated 16 hrs under reflux. The mixture was cooled and reduced *in vacuo*. The residue was taken up in ethyl acetate and washed with saturated aq $NaHCO_3$, followed by saturated aq NaCl. The EtOAc extracts were dried over $MgSO_4$ and reduced *in vacuo*. The ester was used without further purification.

Characteristic NMR Resonances: ^1H NMR 400MHz ($CDCl_3$); 6.76 (Aromatic ABq, 4H), 4.56 (s, 2H), 3.78 (s, 3H). MS CI NH_3 $M+NH_4^+$ = 200. MW = 182.1

Step 2: Preparation of 4-(3-(2-propyl-3-hydroxy-4-acetyl-phenoxy)propyloxy)phenoxy acetic acid

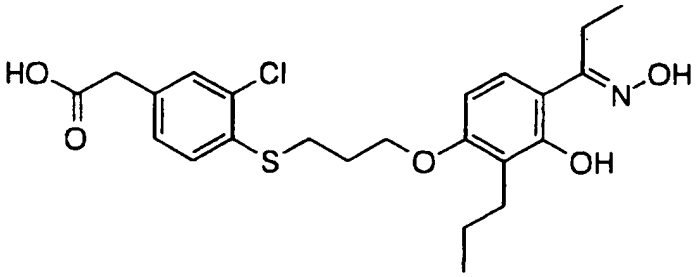
To a solution of 2,4-dihydroxy-3-propylacetophenone (4.0 g, 20.6 mmol) in 2-butanone (50 mL) was added K_2CO_3 (6.0 g) and 1,3-dibromopropane (10 mL). The reaction was heated to reflux until TLC analysis indicated that the reaction was complete. The reaction

was filtered and concentrated to a small volume. Column chromatography (0→10% ethyl acetate/hexanes) gave 1-bromo-3-(2-propyl-3-hydroxy-4-acetyl-phenoxy)propane. To a solution of methyl 4-hydroxyphenoxyacetate Step 1 (156 mg) and 1-bromo-3-(2-propyl-3-hydroxy-4-acetyl-phenoxy)propane (above; 300mg) in 2-butanone (5mL) was added potassium carbonate (196 mg). The mixture was refluxed for 48h. The reaction mixture was cooled to room temperature and partitioned between diethyl ether and 2N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. Column chromatography (30% ethyl acetate/hexanes) gave methyl 4-(3-(2-propyl-3-hydroxy-4-acetyl-phenoxy)propyloxy) phenoxy acetate. A solution of methyl 4-(3-(2-propyl-3-hydroxy-4-acetyl-phenoxy)propyloxy) phenoxy acetate (above; 100 mg) in 3:1:1 methanol / water / tetrahydrofuran (4 mL) was treated with $LiOH.H_2O$ (100 mg). The solution was stirred for 2 hour. The solution was partitioned between ethyl acetate and 2N HCl. The organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid.

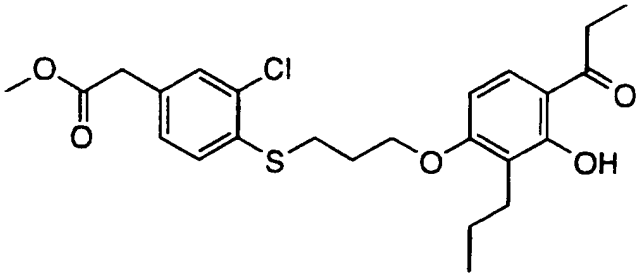
Characteristic NMR Resonances; ^1H NMR (acetone): 7.77 (d, 1H, J = 8.8 Hz); 6.89 (bs, 4H); 6.67 (d, 1H, J = 8.9 Hz); 4.62 (bs, 2H); 4.30 (t, 2H, J = 6.1 Hz); 4.18 (t, 2H, J = 6.0 Hz); 2.62 (bt, 2H, J = 7.4 Hz); 2.58 (s, 3H).

EXAMPLE 8

Preparation of 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyliminopropyl)phenoxy)-propylthio)phenylacetic acid (Compound B):



Step 1: Preparation of:



Methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-propionylphenoxy)-propylthio)-phenylacetate

Step A: Preparation of 1-bromo-3-(2-propyl-3-hydroxy-4-propionyl-phenoxy)propane

A solution of 3-propyl-2,4-dihydroxypropiophenone (25.545 grams) in 2-butanone (300 mL) was treated with 1,3-dibromopropane (48.79 mL) and potassium carbonate (50.859 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was chromatographed over silica gel with hexane/methylene chloride (2:1) to afford the title compound.

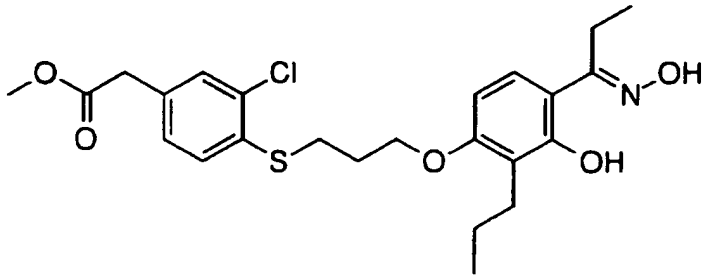
NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 8.8 Hz), 6.43 (d, 1H, J = 8.8 Hz), 4.16 (t, 2H, J = 5.8 Hz), 3.60 (t, 2H, J = 6.4 Hz), 2.94 (quart, 2H, J = 7.3 Hz), 2.61 (bt, 2H, J = 7.5 Hz).

Step B: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-propionylphenoxy)propylthio)-phenylacetate

A solution of 3-chloro-4-dimethylcarbamoylthiophenylacetic acid methyl ester (33.038 grams) in dry methanol (350 mL) was treated with a solution of sodium methoxide in methanol (25wt%; 34.15 mL). The solution was refluxed for 2 hours. HPLC analysis showed the disappearance of the carbamate. The solution was allowed to cool to 50°C. 1-bromo-3-(2-propyl-3-hydroxy-4-propionylphenoxy)propane (31.5 grams) was added and the solution stirred for 1 hour. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once more with pH 4 buffer, then water. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was applied to a silica gel column packed with hexane/methylene chloride (2:1). The column was eluted with this mobile phase until the product began to appear in the eluant. The mobile phase was switched to 100% methylene chloride and elution continued until all the product was recovered.

NMR (Acetone) δ 7.81 (d, 1H, J = 9.1 Hz), 7.25 (dd, 1H, J = 8.1, 1.8 Hz), 6.62 (d, 1H, J = 9.1 Hz), 4.27 (t, 2H, J = 5.9 Hz), 3.64 (s, 3H), 3.25 (t, 2H, J = 7.5 Hz), 3.04 (quart, 2H, J = 7.3 Hz), 2.65 (bt, 2H, J = 7.6 Hz).

Step 2: Preparation of:



Methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyliminopropyl)phenoxy)propylthio)phenylacetate

A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-propionylphenoxy)propylthio)phenylacetate (25.655 grams) in dry methanol (260 mL) was treated with hydroxylamine hydrochloride (3.833 grams). Anhydrous sodium acetate (4.524 grams) was added and the mixture refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 7 buffer. The organic phase was washed once with water and dried over magnesium sulfate, filtered and evaporated to give the title compound as an oil.
NMR ($CDCl_3$) δ 7.11 (dd, 1H, J = 8.1, 1.8 Hz), 6.42 (d, 1H, J = 8.9 Hz), 4.09 (t, 2H, J = 5.7 Hz), 3.68 (s, 3H), 3.14 (t, 2H, J = 7.2 Hz), 2.83 (quart, 2H, J = 7.7 Hz), 2.66 (bt, 2H, J = 7.7 Hz).

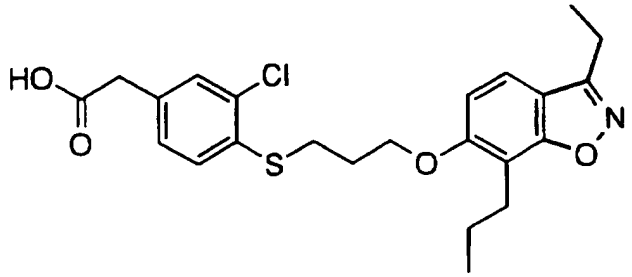
Step 3: Preparation of 3-Chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyliminopropyl)phenoxy)-propylthio)phenylacetic acid (Compound B)

A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyiminopropyl)phenoxy)propylthio)phenylacetate (21.15 grams) in methanol (250 mL) was treated with a solution of lithium hydroxide in water (1.299 M; 67.84 mL). The reaction was refluxed 1 hour. The reaction mixture was partitioned between isopropyl acetate and 0.1N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to a solid. The solid was dissolved in methylene chloride (80 mL) and heated to reflux. Cyclohexane (80 mL) was

added dropwise. The solution was cooled to 0°C and the title compound was isolated by filtration.
NMR ($CDCl_3$) δ 7.11 (dd, 1H, J = 8.1, 1.8 Hz), 6.42 (d, 1H, J = 8.9 Hz), 4.09 (t, 2H, J = 5.7 Hz), 3.13 (t, 2H, J = 7.2 Hz), 2.82 (quart, 2H, J = 7.7 Hz), 2.64 (bt, 2H, J = 7.7 Hz).

EXAMPLE 9

Preparation of 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid (Compound C):



Step 1: Preparation of 1-bromo-3-(2-hydroxy-3-propyl-4-propionylphenoxy)propane

A solution of 2,4-dihydroxy-3-propylphenyl ethyl ketone (25.545 grams) in 2-butanone (300 mL) was treated with 1,3-dibromopropane (48.79 mL) and potassium carbonate (50.859 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was chromatographed over silica gel with hexane/methylene chloride (2:1) to afford the title compound.

NMR ($CDCl_3$) δ 7.62 (d, 1H, J = 8.8 Hz), 6.43 (d, 1H, J = 8.8 Hz), 4.16 (t, 2H, J = 5.8 Hz), 3.60 (t, 2H, J = 6.4 Hz), 2.94 (quart, 2H, J = 7.3 Hz), 2.61 (bt, 2H, J = 7.5 Hz).

Step 2: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-propionylphenoxy)propylthio)phenylacetate

A solution of 3-chloro-4-dimethylcarbamoylthio-phenylacetic acid methyl ester (33.038 grams) in dry methanol (350 mL) was treated with a solution of sodium methoxide in methanol (25wt%; 34.15 mL). The solution was refluxed for 2 hours. HPLC analysis showed the disappearance of the carbamate. The solution was allowed to cool to 50°C. 1-bromo-3-(2-hydroxy-3-propyl-4-propionylphenoxy)propane (31.500 grams) was added and the solution stirred for 1 hour. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once more with pH 4 buffer, then water. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was applied to a silica gel column packed with hexane/methylene chloride (2:1). The column was eluted with this mobile phase until the product began to appear in the eluant. The mobile phase was switched to 100% methylene chloride and elution continued until all the title compound was recovered.
NMR (Acetone) δ 7.81 (d, 1H, J = 9.1 Hz), 7.25 (dd, 1H, J = 8.1, 1.8 Hz), 6.62 (d, 1H, J = 9.1 Hz), 4.27 (t, 2H, J = 5.9 Hz), 3.64 (s, 3H), 3.25 (t, 2H, J = 7.5 Hz), 3.04 (quart, 2H, J = 7.3 Hz), 2.65 (bt, 2H, J = 7.6 Hz).

Step 3: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyiminopropyl)phenoxy)propylthio)-phenylacetate

A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-propionylphenoxy)propylthio)phenylacetate (25.655 grams) in dry methanol (260 mL) was treated with hydroxylamine hydrochloride

(3.833 grams). Anhydrous sodium acetate (4.524 grams) was added and the mixture refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 7 buffer. The organic phase was washed once with water and dried over magnesium sulfate, filtered and evaporated to an oil. The title compound was used without further purification.

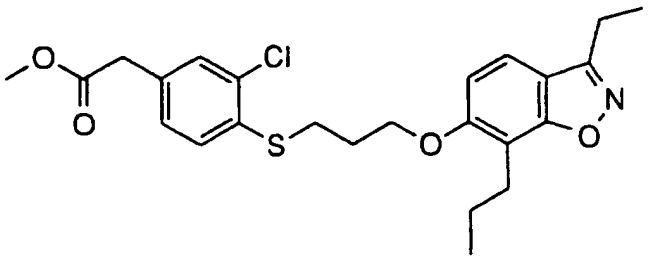
NMR ($CDCl_3$) δ 7.11 (dd, 1H, J = 8.1, 1.8 Hz), 6.42 (d, 1H, J = 8.9 Hz), 4.09 (t, 2H, J = 5.7 Hz), 3.68 (s, 3H), 3.14 (t, 2H, J = 7.2 Hz), 2.83 (quart, 2H, J = 7.7 Hz), 2.66 (bt, 2H, J = 7.7 Hz).

Step 4: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-acetoxyiminopropyl)phenoxy)propylthio)phenylacetate

A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyiminopropyl)phenoxy)propylthio)phenylacetate (5.96 grams) in acetic anhydride (50 mL) was stirred for 16 hours. The solvent was removed *in vacuo*. The remaining residue was dissolved in isopropyl acetate and washed with pH 7 buffer. The organic phase was dried over magnesium sulfate, filtered and evaporated. The title compound was used without further purification.

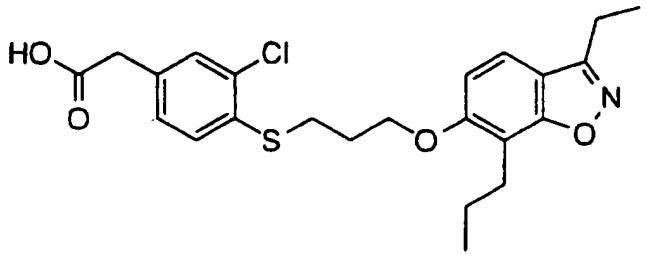
NMR ($CDCl_3$) δ 7.11 (dd, 1H, J = 8.0, 1.9 Hz), 6.44 (d, 1H, J = 8.8 Hz), 4.10 (t, 2H, J = 5.7 Hz), 3.68 (s, 3H), 3.13 (t, 2H, J = 7.2 Hz), 2.86 (quart, 2H, J = 7.6 Hz), 2.67 (bt, 2H, J = 7.6 Hz), 2.22 (s, 3H).

Step 5: Preparation of methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate



A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-acetoxyiminopropyl)phenoxy)propylthio)phenylacetate (6.19 grams) in dry pyridine (65 mL) was refluxed for 3 hours. The solvent was removed *in vacuo* and the residue partitioned between isopropyl acetate and 0.1N HCl. The organic was washed once more with 0.1N HCl. The organic was dried over magnesium sulfate, filtered and evaporated to an oil. The crude product was placed on a silica gel column and eluted with hexane/CH_2Cl_2 (1:1) until the product appeared in the eluant. The mobile phase was changed to 100% CH_2Cl_2 and elution continued until all the title compound was recovered.
NMR ($CDCl_3$) δ 7.38 (d, 1H, J = 8.6 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.87 (d, 1H, J = 8.6 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.68 (s, 3H), 3.16 (t, 2H, J = 7.1 Hz), 2.94 (quart, 2H, J = 7.6 Hz), 2.85 (bt, 2H, J = 7.5 Hz).

Step 6: Preparation of 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid (Compound C)

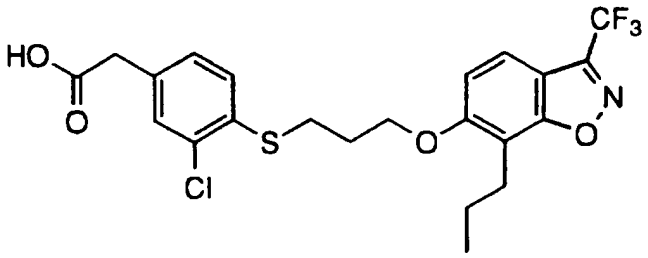


A solution of methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate (4.95 grams) in methanol (95 mL) was treated with a solution of LiOH in water (1.299 M; 16.50 mL). The solution was refluxed for 1 hour. The solution was partitioned between isopropyl acetate and 0.1N HCl. The organic layer was dried over magnesium sulfate, filtered and evaporated to a solid. The solid was suspended in methylene chloride (18 mL) and heated to reflux. Cyclohexane (18mL) was added dropwise while

refluxing. The solution was cooled to 0°C and the title compound isolated by filtration.
NMR ($CDCl_3$) δ 7.38 (d, 1H, J = 8.7 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.87 (d, 1H, J = 8.7 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.57 (s, 2H), 3.16 (t, 2H, J = 7.1 Hz), 2.94 (quart, 2H, J = 7.6 Hz), 2.85 (bt, 2H, J = 7.5 Hz).

EXAMPLE 10

Preparation of 3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid (Compound D):



Step 1: Preparation of 2,4-dihydroxy-3-propyl-trifluoroacetophenone

A solution of 2-propylresorcinol (5.0 grams) and trifluoroacetic anhydride (9.6 mL) in 1,2-dichloroethane (30.0 mL) was treated with aluminum chloride(4.38 grams). This mixture was stirred overnight. The reaction mixture was partitioned between methylene choride and water. The organic phase was dried over sodium sulfate and filtered. The solvent was evaporated and the resulting solid was recrystalized using methylene chloride and cyclohexane (1:1) to give the titled compound.
NMR ($CDCl_3$) δ 7.59 (d, 1H), 6.24 (d, 1H), 5.92 (s, 1H), 2.63 (t, 2H), 1.74 (s, 1H), 1.58 (m, 2H), 0.98 (t, 3H).

Step 2: Preparation of 3-trifluoromethyl-7-propyl-6-hydroxy-benzisoxazole

A mixture of 2,4-dihydroxy-3-propyl-trifluoroacetophenone(2.5 grams), sodium acetate (4.18 grams), hydroxylamine hydrochloride (3.59 grams) and methanol (80 mL) was refluxed overnight. The solvent was then evaporated and the resulting solid was partitioned in ethyl acetate and pH 7 buffer. The organic phase was seperated and washed with brine. The organic phase was dried over sodium sulfate and the solvent was evaporated to give a oil. The oil was then dissolved in acetic anhydride. The solution was stirred for two hours, then the acetic anhydride was evaporated in vacuo. The residue was partitioned between ethyl acetate and pH 7 buffer and the organic phase was dried over sodium sulfate. The organic phase was evaporated to give an oil. This was dissolved in pyridine and refluxed overnight. The solvent was evaporated in vacuo to give an oil which was chromatographed on silica gel using ethyl acetate and hexane (1:4) to give the titled compound.
NMR ($CDCl_3$) δ 7.46 (d, 1H), 6.92 (d, 1H), 5.42 (bs, 1H), 2.89 (t, 2H), 1.74 (m, 2H), 0.98 (t, 3H).

Step 3: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz- [4,5]-isoxazoloxy)propylthio) phenylacetic acid

A solution of 3-trifluoromethyl-7-propyl-6-hydroxy-benzisoxazole (2.5 grams) in 2-butanone (30 mL) was treated with 1,3-dibromopropane (4.8 mL) and potassium carbonate (5.0 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was flitered through a silica gel plug using methylene chloride and hexane (1:2) to give 3-trifluoromethyl-7-propyl-6-(3-bromopropyloxy)-benzisoxazole. A

solution of 3-chloro-4-dimethylcarbamoylthio-phenylacetic acid methyl ester (0.33 grams) in dry methanol (3.5 mL) was treated with a solution of sodium methoxide in methanol (25wt%; 0.341mL). The solution was refluxed for 2 hours. HPLC analysis showed the disappearance of the carbamate. The solution was allowed to cool to 50°C. 3-trifluoromethyl-7-propyl-6-(3-bromopropyloxy)-benzisoxazole (0.31 grams) was added and the solution stirred for 1 hour. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once more with pH 4 buffer, then water. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was applied to a silica gel column packed with hexane/methylene chloride (2:1). The column was eluted with this mobile phase until the product began to appear in the eluant. The mobile phase was switched to 100% methylene chloride and elution continued until all the product was recovered.

NMR ($CDCl_3$) δ 7.52 (d, 2H), 7.30 (d, 1H), 7.27 (d, 1H), 7.12 (d, 1H), 7.08 (d, 1H), 4.21 (t, 2H), 3.68 (s, 3H), 3.54 (s, 2H), 3.15 (t, 2H), 2.89 (t, 2H), 2.19 (m, 2H), 1.68 (m, 2H), 0.94 (t, 3H).

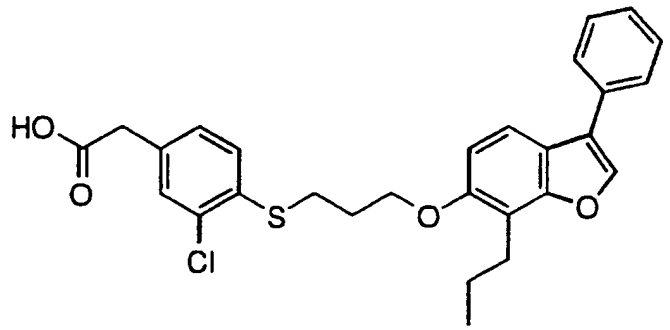
Step 4: Preparation of 3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid (Compound D)

A solution of methyl 3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid (0.113 grams) in methanol (1.5 mL) was treated with a solution of lithium hydroxide in water (1.01 M; 0.362 mL). The reaction was refluxed 1 hour. The reaction mixture was partitioned between isopropyl acetate and 0.1N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to a solid. The solid was suspended in methylene chloride/cyclohexane (1:1; 2 mL). The mixture was refluxed briefly and cooled to 0°C. The title compound was isolated by filtration.

NMR ($CDCl_3$) δ 7.53(d, 2H), 7.31 (d, 1H), 7.27 (d, 1H), 7.12 (d, 1H), 7.02 (d, 1H), 4.21 (t, 2H), 3.57 (s, 2H), 3.16 (t, 2H), 2.89 (t, 2H), 2.19 (m, 2H), 1.67 (m, 2H), 0.93 (t, 3H).
ESI-MS: m/e = 488 (m+1).

EXAMPLE 11

Preparation of 3-chloro-4-(3-(3-phenyl-7-propylbenzofuran-6-yloxy)propylthio)-phenylacetic acid (Compound E):



Step 1: Preparation of 2-propyl-3-(2-phenyl-2-oxoethoxy)phenol

To a solution of 2-propyl resorcinol (178.27 g; 1.171 mol) in dry DMF (dimethylformamide) (1200 mL) was added Cessium carbonate (104.95 g; 322.12 mmol). The mixture was stirred at room temperature and treated dropwise with a solution of 2-bromoacetophenone (58.29 G; 292.84 mmol) in dry DMF (500 mL) over 2 hours. The was stirred at ambient temperature for 64 hours. The reaction mixture was partitioned between isopropyl acetate and water. The aqueous was adjusted to pH 13 by addition of aq. 5 N sodium hydroxide. The organic was dried over magnessium sulfate, filtered and evaperated to a residue. The residue was disolved in methylene chloride (110 mL) and hexane (350 mL) and heated to reflux. The solution was cooled to -10°C. Stirring was continued for 1 hour. The title compound was recovered by filtration.

^{1}H NMR(400MHz, $CDCl_3$): δ 8.00 (dd, J = 7.3, 1.3 Hz, 2H), 7.59 (t, J = 7.2, 1.4 Hz, 1H), 7.49 (dt, J = 7.6, 1.5 Hz, 2H), 6.98 (t, J = 8.2 Hz, 1H), 6.47 (d, J = 8.1 Hz, 1H), 6.38 (d, J = 8.2 Hz, 1H), 4.75 (s, very broad, 1H), 2.66 (t, J = 7.7 Hz, 2H), 1.57 (hex, J = 7.5 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H).

Step 2: Preparation of 3-phenyl-6-hydroxy-7-propylbenzofuran

To a stirred suspension of 2-propyl-3-(2-phenyl-2-oxoethoxy)phenol (9.30 g) in o-phosphoric acid (85%) (93 mL) at room temperature was added over a 45 minutes period phosphorus pentoxide (46.50 g). During this period the reaction mixture was heated several times with a heat gun. After stirring the mixture for 30 minutes the reaction was checked by TLC (thin layer chromatography - take a little of sample with a capillary and dissolve sample in water and add several drops of ether; elution: 50% methylene chloride in hexane). The reaction mixture was heated again with a heat gun if the reaction was not complete. The reaction mixture continued to be stirred for 20 minutes, then was poured into a beaker containing ice. The reaction flask was then rinsed with water and ether, and the washings were added to the beaker. The organic layer was separated, washed with water, dried over MgSO4, and concentrated. Column chromatography(silica gel 60, 50% methylene chloride in hexane) gave the title compound. ^{1}H NMR(400MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.64 (dd, J = 7.0, 1.4 Hz, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.46 (dt, J = 7.3, 1.8 Hz, 2H), 7.35 (dt, J = 7.2, 1.3 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 4.74 (s, very broad, 1H), 2.90 (t, J = 7.7 Hz, 2H), 1.75 (hex, J = 7.5 Hz, 2H), 1.03 (t, J= 7.4 Hz, 3H).

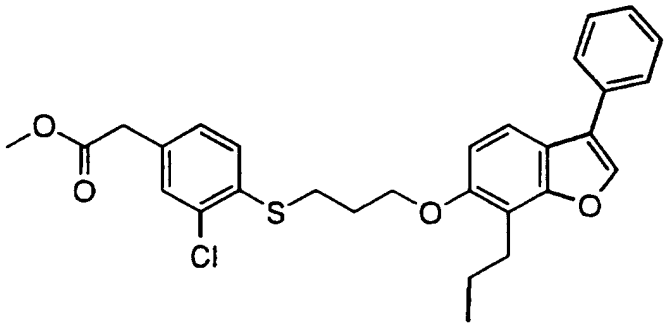
Step 3: Preparation of 3-phenyl-6-(3-bromopropyloxy)-7-propylbenzofuran

To a solution of 3-phenyl-6-hydroxy-7-propylbenzofuran (3.54 g, 13.99 mmol) and potassium carbonate (2.08 g, 15.05 mmol) in

dry methyl ethyl ketone (50 ml) was added 1,3-dibromopropane (2.84 ml, 27.98 mmol). The reaction mixture refluxed for 5 hours under nitrogen. The mixture was partitioned between isopropyl acetate and pH4 buffer. The organic was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, 50% methylene chloride in hexane) to afford the title compound.

^{1}H NMR(400MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.62 (dd, J = 7.0, 1.4 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.44 (td, J = 6.8, 1.6 Hz, 2H), 7.35 (dd, J = 7.0, 1.4 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 4.16 (t, J = 5.8 Hz, 2H), 3.65 (t, J = 6.4 Hz, 2H), 2.88 (t, J = 6.2 Hz, 2H), 2.36 (quint, J = 6.3 Hz, 2H), 1.70 (hex, J = 6.1 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H).

Step 4: Preparation of Methyl 3-chloro-4-(3-(3-phenyl-7-propylbenzofuran-6-yloxy)propylthio)phenylacetate



To a solution of 3-chloro-4-dimethylcarbomoylthio-benzene-acetic acid, methyl ester (3.88 g, 13.50 mmol) and methanol (40 ml), was added 4.37M sodium methoxide (3.35 ml, 14.63 mmol). The reaction mixture was refluxed for 2 hr, was then allowed to cool to 50°C. 3-phenyl-6-(3-bromopropyloxy)-7-propylbenzofuran (4.20 g, 11.25 mmol) was added , and the mixture was stirred at 50°C for 1.5 hr. The mixture was partitioned between isopropyl acetate and pH4 buffer. The organic was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by

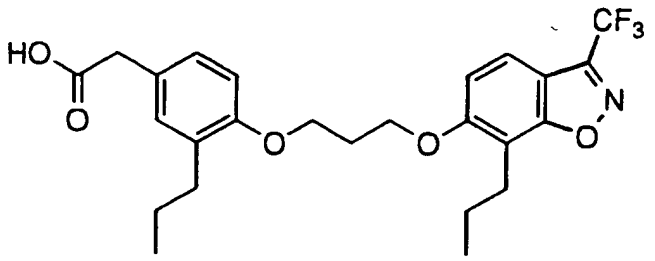
chromatography (silica gel, 50% methylene chloride in hexane) to afford the title compound.
^{1}H NMR(400MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.60 (dd, J = 8.3, 1.2 Hz, 2H), 7.53 (d, J = 8.3, Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.34 (dd, J = 8.4, 1.3 Hz, 1H), 7.28 (m, 2H), 7.11 (dd, J = 8.2, 1.7 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 3.69 (s, 3H), 3.55 (s, 2H), 3.17 (t, J = 7.0 Hz, 2H), 2.89 (t, J = 7.4 Hz, 2H), 2.18 (quint, J = 7.1 Hz, 2H), 1.71 (hex, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H).

Step 5: Preparation of 3-chloro-4-(3-(3-phenyl-7-propylbenzofuran-6-yloxy)propylthio)phenylacetic acid (Compound E)

To a solution of methyl 3-chloro-4-(3-(3-phenyl-7-propylbenzofuran-6-yloxy)propylthio)phenylacetate (3.72 g, 7.31 mmol) prepared in last step and aqueous lithium hydroxide(1.0 M; 14.62 ml; 14.62 mmol) in methanol (25 ml) was refluxed for 1 hr. The mixture was partationed beteen isopropyl acetate and pH4 buffer. The organic was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, 50% methylene chloride in hexane) to afford the title compound. M.P: 143°C. ESI-MS: m/e- 495(M+1)
^{1}H NMR(400MHz, $CDCl_3$): δ 7.7o (s, 1H), 7.61 (dd, J = 8.3, 1.2 Hz, 2H), 7.54 (d, J = 8.4, Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.35 (dd, J = 8.4, 1.3 Hz, 1H), 7.29 (m, 2H), 7.11 (dd, J = 8.1, 1.8 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 4.15 (t, J = 5.8 Hz, 2H), 3.57 (s, 2H), 3.17 (t, J = 7.0 Hz, 2H), 2.89 (t, J = 7.4 Hz, 2H), 2.18 (quint, J = 7.1 Hz, 2H), 1.71 (hex, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H).

EXAMPLE 12

Preparation of 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid (Compound F):



Step 1: Preparation of methyl 4-alloxyphenylacetate

A solution of methyl 4-hydroxyphenylacetate (3.2 grams) in 2-butanone (70 mL) was treated with allyl bromide (2.0 mL) and potassium carbonate (3.5 grams). The mixture was refluxed overnight. The reaction mixture was cooled to room temperature and partitioned between isopropyl acetate and pH 4 buffer. The organic layer was separated, washed with water, dried over MgSO4, and concentrated. Column Chromatography (silica gel 60, 50% methylene chloride in hexane) gave the title compound.

^{1}H NMR(400MHz, $CDCl_3$): δ 7.16 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 6.04 (m, 1H), 5.4-5.2 (m, 2H), 4.5 (m, 2H), 3.66 (s, 3H), 3.54 (s, 2H).

Step 2: Preparation of methyl 3-allyl-4-hydroxyphenylacetate

A solution of methyl 4-alloxyphenylacetate (3.1 grams) in dry ortho-dichlorobenzene (50 mL) was refluxed for 25 hours. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, 50% methylene chloride in hexane) to afford the title compound.

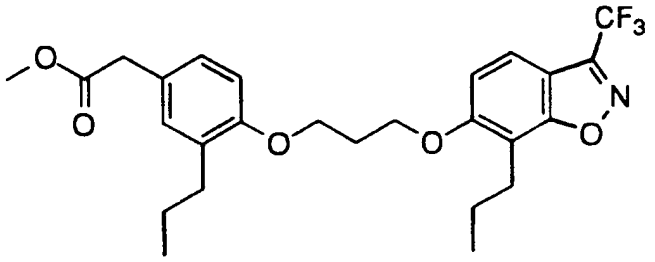
^{1}H NMR(400MHz, $CDCl_3$): δ 7.01 (m, 2H), 6.71 (d, 1H, J = 7.4 Hz), 5.27 (s, 1H), 5.12 (m, 2H), 3.67 (s, 3H), 3.52 (s, 2H), 3.35 (m, 2H).

Step 3: Preparation of methyl 3-propyl-4-hydroxyphenylacetate

A solution of methyl 3-allyl-4-hydroxyphenylacetate (1.71 grams) and palladium (10 wt.% on activated carbon) (0.27 grams) in ethyl acetate (30 mL) was hydrogenated at 50 PSI for 2 hours. The reaction mixture was filtered and concentrated to afford the title compound.

^{1}H NMR(400MHz, $CDCl_3$): δ 6.99 (d, 1H, J = 2.2 Hz), 6.95 (dd, 1H, J = 8.1, 2.2 Hz), 6.67 (d, 1H, J = 8.1 Hz), 4.83 (s, 1H), 3.66 (s, 3H), 3.51 (s, 2H), 2.53 (t, 2H, J = 7.6 Hz), 1.61 (hex, 2H, J = 7.5 Hz), 0.95 (t, 3H, J = 7.3 Hz).

Step 4: Preparation of methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate



A solution of methyl 3-propyl-4-hydroxyphenylacetate (0.10 grams), 3-trifluoromethyl-7-propyl-6-(3-bromopropyloxy)-benzisoxazole (0.21 grams) and potassium carbonate (0.07 grams) in 2-butanone (4 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and partitioned between isopropyl acetate and pH 4 buffer. The organic layer was separated, washed with water, dried over MgSO4, and concentrated. Column Chromatography (silica gel 60, 50% methylene chloride in hexane) gave the title compound.

^{1}H NMR(400MHz, $CDCl_3$): δ 7.53 (d, 1H, J = 8.8 Hz), 7.03 (d, 1H, J = 8.9 Hz), 7.01 (m, 2H), 6.78 (d, 1H, J = 8.3 Hz), 4.30 (t, 2H, J = 6.1 Hz), 4.16 (t, 2H, J = 6.0 Hz), 3.65 (s, 3H), 3.52 (s, 2H), 2.87 (t, 2H, J = 7.5 Hz), 2.53 (t, 2H, J = 7.6 Hz), 2.32 (quint, 2H, J = 6.1 Hz), 1.66 (hex,

2H, J = 7.6 Hz), 1.55 (hex, 2H, J = 7.5 Hz), 0.91 (t, 3H, J = 7.3 Hz), 0.87 (t, 3H, J =7.3 Hz).

Step 5: Preparation of 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid (Compound F)

A solution of methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate (0.08 grams) in methanol (3 mL) was treated with a solution of LiOH in water (1.0 M, 0.32 mL). The solution was refluxed for 1 hour. The solution was partitioned between isopropyl acetate and 0.2 N HCl. The organic layer was separated, washed with water, dried over MgSO4, and concentrated to afford the title compound.

^{1}H NMR(400MHz, $CDCl_3$): δ 7.53 (d, 1H, J = 8.8 Hz), 7.05 (d, 1H, J = 8.8 Hz), 7.02 (m, 2H), 6.79 (d, 1H, J = 8.3 Hz), 4.29 (t, 2H, J = 6.1 Hz), 4.16 (t, 2H, J = 6.0 Hz), 3.54 (s, 2H), 2.88 (t, 2H, J = 7.5 Hz), 2.52 (t, 2H, J = 7.6 Hz), 2.33 (quint, 2H, J = 6.1 Hz), 1.67 (hex, 2H, J = 7.6 Hz), 1.54 (hex, 2H, J = 7.5 Hz), 0.90 (t, 3H, J = 7.3 Hz), 0.86 (t, 3H, J =7.3 Hz).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the instant invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in

accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound useful for raising the plasma level of high density lipoprotein in a mammal which is a PPARδ agonist.

2. The compound of Claim 1 which has an IC_{50} equal to or less than 10 μM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 μM in the hPPARδ transactivation assay.

3. The compound of Claim 2 which has an IC_{50} equal to or less than 100 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 100 nM in the hPPARδ transactivation assay.

4. The compound of Claim 3 which has an IC_{50} equal to or less than 50 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 50 nM in the hPPARδ transactivation assay.

5. The compound of Claim 4 which has an IC_{50} equal to or less than 10 nM in the hPPARδ binding assay and an EC_{50} equal to or less than 10 nM in the hPPARδ transactivation assay.

6. A method for raising the plasma level of high density lipoprotein in a mammal comprising administering to the mammal a high density lipoprotein-raising amount of the PPARδ agonist compound of claim 1.

7. A method for raising the plasma level of high density lipoprotein in a mammal comprising administering to the mammal a high density lipoprotein-raising amount of the compound of claim 2.

8. A method for raising the plasma level of high density lipoprotein in a mammal comprising administering to the mammal a high density lipoprotein-raising amount of the compound of claim 3.

9. A method for raising the plasma level of high density lipoprotein in a mammal comprising administering to the mammal a high density lipoprotein-raising amount of the compound of claim 4.

10. A method for raising the plasma level of high density lipoprotein in a mammal comprising administering to the mammal a high density lipoprotein-raising amount of the compound of claim 5.

11. The method of Claim 6 wherein the mammal is a human.

12. The method of Claim 11 wherein the human is at risk for developing atherosclerosis or having an atherosclerotic disease event.

13. The method of Claim 11 wherein the human has atherosclerosis.

14. The method of Claim 6 further comprising the administration of the PPARδ agonist compound in combination with a therapeutically effective amount of one or more additional active agents selected from the group consisting of: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; and aspirin.

15. The method of Claim 14 wherein the additional active agent is a cholesterol biosynthesis inhibitor.

16. The method of Claim 15 wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

17. The method of Claim 16 wherein the HMG-CoA reductase inhibitor is selected from the pharmaceutically acceptable lactone, free acid, ester and salt forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin.

18. The method of Claim 17 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

19. A method for reducing the risk of developing atherosclerosis or having an atherosclerotic disease event comprising administering a prophylactically effective amount of the PPARδ agonist compound of claim 1 to a mammal at risk of developing atherosclerosis or having an atherosclerotic disease event.

20. A method for reducing the risk of developing atherosclerosis or having an atherosclerotic disease event comprising administering a prophylactically effective amount of the PPARδ agonist compound of claim 2 to a mammal at risk of developing atherosclerosis or having an atherosclerotic disease event.

21. A method for reducing the risk of developing atherosclerosis or having an atherosclerotic disease event comprising administering a prophylactically effective amount of the PPARδ agonist compound of claim 3 to a mammal at risk of developing atherosclerosis or having an atherosclerotic disease event.

22. A method for reducing the risk of developing atherosclerosis or having an atherosclerotic disease event comprising

administering a prophylactically effective amount of the PPARδ agonist compound of claim 4 to a mammal at risk of developing atherosclerosis or having an atherosclerotic disease event.

23. A method for reducing the risk of developing atherosclerosis or having an atherosclerotic disease event comprising administering a prophylactically effective amount of the PPARδ agonist compound of claim 5 to a mammal at risk of developing atherosclerosis or having an atherosclerotic disease event.

24. The method of Claim 19 wherein the mammal is a human.

25. The method of Claim 24 wherein the human is at risk for developing atherosclerosis.

26. The method of Claim 24 wherein the human is at risk for having an atherosclerotic disease event .

27. The method of Claim 19 further comprising the administration of the PPARδ agonist compound in combination with a prophylactically effective amount of one or more additional active agents selected from the group consisting of: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; and aspirin.

28. The method of Claim 27 wherein the additional active agent is a cholesterol biosynthesis inhibitor.

29. The method of Claim 28 wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

30. The method of Claim 29 wherein the HMG-CoA reductase inhibitor is selected from the pharmaceutically acceptable lactone, free acid, ester and salt forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin.

31. The method of Claim 30 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

32. A method for treating atherosclerosis comprising administering a therapeutically effective amount of the PPARδ agonist compound of claim 1 to a mammal who has atherosclerosis.

33. A method for treating atherosclerosis comprising administering a therapeutically effective amount of the PPARδ agonist compound of claim 2 to a mammal who has atherosclerosis.

34. A method for treating atherosclerosis comprising administering a therapeutically effective amount of the PPARδ agonist compound of claim 3 to a mammal who has atherosclerosis.

35. A method for treating atherosclerosis comprising administering a therapeutically effective amount of the PPARδ agonist compound of claim 4 to a mammal who has atherosclerosis.

36. A method for treating atherosclerosis comprising administering a therapeutically effective amount of the PPARδ agonist compound of claim 5 to a mammal who has atherosclerosis.

37. The method of Claim 32 wherein the mammal is a human.

38. The method of Claim 32 further comprising the administration of the PPARδ agonist compound in combination with a therapeutically effective amount of one or more additional active agents selected from the group consisting of: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; and aspirin.

39. The method of Claim 38 wherein the additional active agent is a cholesterol biosynthesis inhibitor.

40. The method of Claim 39 wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

41. The method of Claim 40 wherein the HMG-CoA reductase inhibitor is selected from the pharmaceutically acceptable lactone, free acid, ester and salt forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin.

42. The method of Claim 41 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

43. A post-myocardial infarction therapy comprising administering to a human who has suffered a myocardial infarction a high density lipoprotein-raising amount of the PPARδ agonist compound of claim 1.

44. A post-myocardial infarction therapy comprising administering to a human who has suffered a myocardial infarction a high density lipoprotein-raising amount of the PPARδ agonist compound of claim 2.

45. A post-myocardial infarction therapy comprising administering to a human who has suffered a myocardial infarction a high density lipoprotein-raising amount of the PPARδ agonist compound of claim 3.

46. A post-myocardial infarction therapy comprising administering to a human who has suffered a myocardial infarction a high density lipoprotein-raising amount of the PPARδ agonist compound of claim 4.

47. A post-myocardial infarction therapy comprising administering to a human who has suffered a myocardial infarction a high density lipoprotein-raising amount of the PPARδ agonist compound of claim 5.

48. The method of Claim 43 wherein the human is at risk for having a subsequent atherosclerotic disease event.

49. The method of Claim 43 further comprising the administration of the PPARδ agonist compound in combination with a therapeutically effective amount of one or more additional active agents selected from the group consisting of: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: cholesterol

acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrizol; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; and aspirin.

50. The method of Claim 49 wherein the additional active agent is a cholesterol biosynthesis inhibitor.

51. The method of Claim 50 wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

52. The method of Claim 51 wherein the HMG-CoA reductase inhibitor is selected from the pharmaceutically acceptable lactone, free acid, ester and salt forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin.

53. The method of Claim 52 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

54. A pharmaceutical composition comprising the PPARδ agonist of claim 1 and a pharmaceutically acceptable carrier.

55. The composition of Claim 54 further comprised of one or more additional active agents selected from the group consisting of: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent; a cholesterol biosynthesis inhibitor; an acyl-coenzyme A: cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrizol;

vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; and aspirin.

56. The composition of Claim 55 wherein the additional active agent is a cholesterol biosynthesis inhibitor.

57. The composition of Claim 56 wherein the cholesterol biosynthesis inhibitor is an HMG-CoA reductase inhibitor.

58. The composition of Claim 57 wherein the HMG-CoA reductase inhibitor is selected from the pharmaceutically acceptable lactone, free acid, ester and salt forms of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin.

59. The composition of Claim 58 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

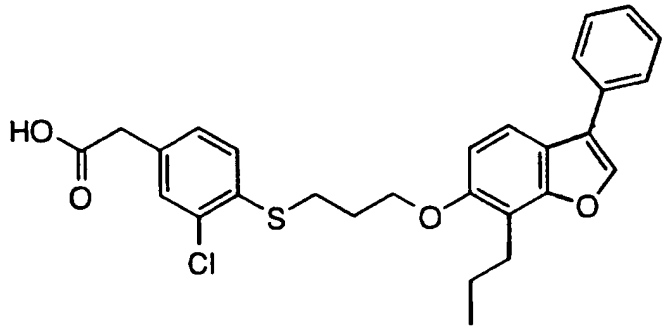
60. A pharmaceutical composition made by combining the PPARδ agonist of claim 1 and a pharmaceutically acceptable carrier.

61. A pharmaceutical composition made by combining the PPARδ agonist of claim 1, an HMG-CoA reductase inhibitor and a pharmaceutically acceptable carrier.

62. A process for making a pharmaceutical composition comprising combining the PPARδ agonist of claim 1 and a pharmaceutically acceptable carrier.

63. A process for making a pharmaceutical composition comprising combining the PPARδ agonist of claim 1, an HMG-CoA reductase inhibitor and a pharmaceutically acceptable carrier.

64. The compound of claim 1 having the following structural formula:



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01808

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 307/79; A61K 31/34
US CL :549/469; 514/469
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/469; 514/469

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN- File Registry and CAPLUS Files

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAPLUS, Abstract No. 110:192564, HAMMOND et al. '2,3-Dihydro-5-benzofuranols as antioxidant-based inhibitors of leukotriene biosynthesis', abstract, J. Med. Chem., 32(5), 1006-20, 1989, see entire abstract.	1-64

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 02 MAY 1997	Date of mailing of the international search report 03 JUN 1997
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